Diabetes:
Treatment and Management

Steven Ferrucci, OD, FAAO
Chief, Optometry Sepulveda VA
Professor, SCCO/MBKU

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What is diabetes?

- DM is a chronic disorder characterized by a lack of insulin or increased resistance to insulin
- Insulin is needed for proper uptake of glucose
- Clinical result is hyperglycemia
  - retinopathy
  - nephropathy
  - neuropathy

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Statistics

- Approximately 9.3% of US population
  - 29.1 Million Americans
  - 2012: 1 out of 10
  - 2050: 1 out of 5 to 1 out of 3
- Almost 1/3 undiagnosed
- Another **79 million** Americans have pre-diabetes and are likely to develop diabetes if do not change habits
  - 37% of adults age 20 or older

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Cost of Care

- ⇧ from $172 Billion in 2007 to $245 Billion in 2012- ⇧41%
  - $ 176 B direct costs
  - $ 69 B indirect
- In CA alone, $24.5 Billion (July 2015)
- Medical cost 2.3X higher in pts with DM
- Care of people with DM accounts for 1 out 5 healthcare dollars in US

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TYPE 1

- Formerly IDDM or juvenile onset
- Prevalence: 0.2%
- 10% of all DM
- Most common age of onset < 30
- Destruction of insulin producing B-cells in pancreas (auto-immune? viral?)
- Total lack of endogenous insulin
- Need to be on insulin to survive

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TYPE 2

- Formerly NIDDM or adult onset
- Prevalence: ≈9.0%
- 90% of all DM
- Most frequent age of onset > 40
- Often asymptomatic
- Characterized by insulin resistance
- Strong genetic predisposition
  - One parent, 50% likelihood
  - Both parents , 80%

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LADA: Type 1.5

- Latent auto-immune diabetes in adults
- Diagnosed in adulthood
  - Over age 40
  - Even in 70s and 80s
- Progression to need for insulin is rapid
  - Often witjhn 5 years
- Pts generally not obsess
- Do not respond to oral meds or lifestyle/dietary changes

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Gestational Diabetes

- **Affects 4% of all pregnancies**
- **High risk populations:**
  - **Pregnant woman greater than age 25**
  - **Abnormal body weight**
  - **Have first degree relatives with diabetes**
  - **Hispanic, Asian, Native American , African American descent**
- **Screen in 24th to 28th week of pregnancy**
- **NO ADDITIONAL RETINAL SCREENING NEEDED**

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Symptoms

- **Often asymptomatic, especially Type 2**
- **Classic symptoms**
  - **polydipsia**
  - **polyphagia**
  - **polyurea**
- **Others: weight loss, delayed wound healing, dry mouth, dry skin, recurrent infections, refractive changes**

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Risk Factors

- **Family history**
- **Specific ethnic backgrounds**
  - **African Americans**
  - **Native Americans**
  - **Hispanic**
  - **Asian American**
  - **Pacific islander**
- **Sedentary Lifestyle**
- Pertinent medical history
  - obesity
  - cardiovascular disease
  - HTN
  - High cholesterol
  - Polycystic ovarian syndrome
  - Psychiatric illness
  - Gestational DM
  - IFG/IGT

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Traditional Diagnosis

- **Fasting blood glucose > 126 mg/dL**
- **OGTT > 200 mg/dL (2 hour sample)**

- **Any random testing >200 mg/dl should be referred for further testing**
- **Random testing > 200 mg/dL with symptoms very suggestive of DM**

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Newer Diagnosis: HgbA1c

- **Tells blood sugar control over 3 months**
  - **normal range 4% to 6%**
  - **6-6.5 Pre-Diabetes**
  - **≥ 6.5 would be indicative of DM**
  - **First major change in 30 years**
  - **In adults and children, not pregnant women**
    - **Advantages:**
      - **Convenience: no fasting**
      - **More accurate: average over 3 months**

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Time in range

- New way to MONITOR BS levels in pts with DM
- % of time a patient's BS is within target values
  - Typically 70-180mg/dl
  - Need CGM
- May be better indicator of BS control than HgbA1c
- 10% Increase in TIR decreased risk of retinopathy by 61%

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Treatment of Type 2 DM

- **Goal: to produce desirable blood glucose levels with minimal adverse effects and maximal patient compliance**
- **Treatment begins with diet and exercise and ends with insulin**
- **Often, adequate control can be achieved with oral agents**
  - **If not, insulin is utilized**

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Medical Management of DM

Oral Agents[1]

DRUG CLASS	EXAMPLES Generic (Trade)
Biguanide	Metformin (Glucophage®)
α-Glucosidase Inhibitors	Acarbose (Precose®), miglitol (Glyset®)
Sulfonylureas	Glipizide (Glucotrol®), glyburide (Micronase®), glimepiride (Amaryl®)
Meglitinides	Repaglinide (Prandin®), nateglinide (Starlix®)
TZDs (glitazones)	Pioglitazone (Actos), rosiglitazone (Avandia®)
DPP-4 Inhibitors (dipeptidyl-peptidase-4 inhibitors)	Sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®), alogliptin (Nesina)
SGLT2 Inhibitors (sodium-glucose cotransporter 2 inhibitors)	Canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®)

1. Author AA, et al. American Association of Clinical Endocrinology guide to physicians: diabetes management algorithm 2015 consensus statement. Endocr Pract. 2015;21(5):516-527.

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Medical Management of DM

Injectable Non-Insulin Agents[1]

DRUG CLASS	EXAMPLES Generic (Trade)
GLP-1 Agonists (incretin mimetics)	Liraglutide (Victoza®), exenatide (Byetta®), exenatide ER (Bydureon®), dulaglutide (Trulicity®), albiglutide (Tanzeum®)
Amylin Analogs	Pramlintide (Symlin®)

1. Author AA, et al. American Association of Clinical Endocrinology guide to physicians: diabetes management algorithm 2015 consensus statement. Endocr Pract. 2015;21(5):516-527.

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Medical Management of DM

Insulin Therapy[1,2]

DRUG CLASS	EXAMPLES Generic (Trade)
Basal Insulin	Glargine (Lantus®), detemir (Levemir®), glargine U-300 (Toujeo®)
Rapid-Acting Insulin Analogs	Aspart (NovoLog®), lispro (Humalog®), glulisine (Apidra®), lispro U-200 (Humalog® U-200)
Premixed Insulin	70:30, 75:25, 50:50 (Humulin®, Novolin®)
Regular Insulin	U-500 (Humulin® R)
Inhaled Insulin	Afrezza

1. Author AA, et al. American Association of Clinical Endocrinology guide to physicians: diabetes management algorithm 2015 consensus statement. Endocr Pract. 2015;21(5):516-527.
2. American Diabetes Association. Insulin basics. http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/insulin-basics.html?referrer=https://www.google.com/. Accessed October 14, 2015.

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Medical Management of DM

Insulin Delivery Devices

INSULIN PUMP THERAPY COMPANY	EXAMPLES
Medtronic	MiniMed® 530G, Paradigm® Revel™
Tandem	t:slim®, t:flex®
Insulet	OmniPod®
Animas®	Vibe™, OneTouch® Ping®
Accu-chek®	Combo

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Current recommendations for Treatment of DM

- Control BS levels
  - HgbA1c < ?
- Control HTN
  - BP<120/80
- Control Cholesterol levels
  - Total cholesterol < 200
- No smoking
- Exercise
- Yearly foot exams, dental exams, and dilated retinal exams

ABC's

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Diabetic Retinopathy

- Leading cause of blindness 20-74 year old
- 8-12% of all new cases of legal blindness
- 50,000 Americans legally blind
- Early diagnosis and treatment can decrease vision loss by 50-60%
- Factors which influence development of DR
  - duration of disease
  - control of BS

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Duration of disease

- Type 1 Pts:
  - Retinopathy rare in 1st 3- 5 years
  - After 10 yrs, 60% have some retinopathy
  - After 20 yrs, almost always present
    - 50-60% PDR
- Type 2:
  - ≈ 20% to 39% have retinopathy at time of diagnosis
  - After 15 years, 60-80% have some retinopathy
    - 20% chance of PDR

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Control of Blood Sugar

- DCCT Trial: 1993
  - Intensive blood glucose control reduced risk of developing retinopathy by 76%
  - Slowed the progression by 54% if already had retinopathy
- UKPDS: 1998
  - for every 1% decrease in HgbA1C there is a 35% reduction in risk for retinopathy
  - 34% reduction in retinopathy progressing with good HTN control

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Diabetic Retinopathy

- Joslin Diabetes Center study
  - Only 60% of DM' s receive "timely eyecare"
  - $624 million and 400,000 patients' sight saved if annual eye exam and appropriate treatment
- March 2001: *Ophthalmology* 35% of DM reported no annual DFE

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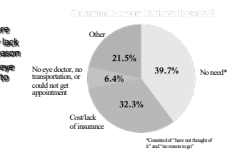
Why Patients Don't Receive Annual Eye Exams

As reported by patients diagnosed with diabetes who are not receiving annual eye exams

- Patients with visual impairments are more likely to cite "cost or lack of insurance" as a reason for not receiving an eye exam and less likely to report "no need"



"Consisted of "have not thought of it" and "no reason to go"

Chou CY, et al. Diabetes Care. 2014;37:1169-1176.

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Diabetic Retinopathy

- Non-proliferative Diabetic Retinopathy (NPDR)
  - mild
  - moderate
  - severe
  - very severe
- Proliferative Diabetic Retinopathy (PDR)
  - Including high-risk

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Nonproliferative Diabetic Retinopathy (NPDR)

- Loss of retinal capillary pericytes
- Weakens capillary walls
- Causes non-perfusion in capillary beds and hypoxia
- Divided into mild, moderate, and severe (and very severe)

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Mild NPDR

- Microaneurysms (ma)
- Dot/blot hemorrhages

- Follow-up: 1 yr
  - 5-10% of pts with no retinopathy will progress to retinopathy within 1 year
  - 5-10% with mild NPDR will also progress within 1 year

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Moderate NPDR

- Marked hemorrhages/ma
- Cotton wool spots (CWS)
- Venous beading (VB)
- Intra-retinal microvascular abnormalities to mild degree (IRMA's)

- Follow Up: 6 months
  - as many as 16% of pts with mod NPDR can progress to proliferative disease within 4 years

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Severe/ Very Severe NPDR

- 4-2-1 Rule:
  - Marked hemes/ma in all 4 quadrants
  - VB in 2 or more quadrants
  - Marked IRMA's in one quadrant
- Very severe: 2 of the 3 above criteria

- Old thinking: Follow-up: 3-4 months
  - Between 10-50% of pts with this level progress to PDR within 1 year
- New Thinking: Strongly consider referral to retina specialist
  - New studies supporting use of anti-VEGF prior to PDR

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Rate of Progression to PDR

	1 yr	5 yr
Mild	5%	14%
Moderate	12-26%	30-48%
Severe	52%	71%

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New thinking

- Must look in periphery
- As much as 30% of hemes, 27% orfIRMAs, and 34% of NVE outside EDTRS fields
- 10% of eyes misclassified level of DR unless peripheral lesion considered
- Also, PPL (predominately priperhal lesions) and NPDR had 4.7 x increased risk of PDR in 4 year's
  - 6% to almost 25%!

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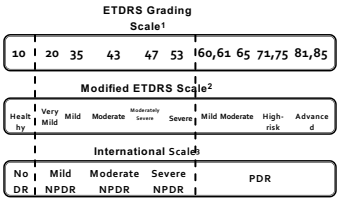
HISTORY OF DR SEVERITY SCALES – ETDRS, MODIFIED ETDRS, AND INTERNATIONAL



1. ETDRS. Ophthalmology. 1991;98:823. 2. Ip et al. Arch Ophthalmol. 2011;130:1145. 3. American Academy of Ophthalmology. www.aoph.org/dynamic/data/channelresources/diabetic-retinopathy-detail.pdf. Accessed April 15, 2018.

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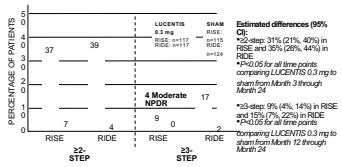
RISE AND RIDE

ETDRS-DRSS STEP IMPROVEMENTS AT 2 YEARS[1]



Estimated differences (95% CI):

- ≥2-step: 31% (21%, 40%) in RISE and 35% (26%, 44%) in RIDE
- *P<0.05 for all time points comparing LUCENTIS 0.3 mg to sham from Month 3 through Month 24*
- ≥3-step: 9% (4%, 14%) in RISE and 15% (7%, 22%) in RIDE
- *P<0.05 for all time points comparing LUCENTIS 0.3 mg to sham from Month 12 through Month 24*

Please see select Important Safety Information provided throughout this presentation and the accompanied full prescribing information.

1. LUCENTIS (ranibizumab) Prescribing Information, 2018.

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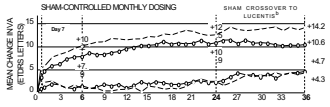
RISE AND RIDE

VISION GAINS THROUGH 2 YEARS, SUSTAINED AT 3 YEARS[1-3]



P<0.01 for all time points comparing LUCENTIS 0.3 mg to sham through 2 years

Following 3 years of monthly therapy, patients were eligible to receive additional injections if needed. During this open label extension,

- The mean number of injections was **4.5 over 14 months**[4]
- **~20% of patients maintained vision** with no further injections through Year 4[4]

LUCENTIS is approved for the treatment of RISE and RIDE. Please see select Important Safety Information provided throughout this presentation and the accompanied full prescribing information.

†At least 12 months of follow-up. Crossover to LUCENTIS 0.3 mg monthly.

1. LUCENTIS (ranibizumab) Prescribing Information, 2018. 2. Data on file, Genentech, Inc. 3. Nguyen et al. Ophthalmology. 2012;119:789. 4. Boyer et al. Ophthalmology. 2015;122:2504.

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Fate of 47

- **In a post hoc study, Pts with moderately severe/severe NPDR (EDTRS 47/53) had a two step regression at 2 years in 78% of pts vs. 12% of sham**
- **Therefore, pts with moderately severe or severe NPDR do very well with treatment**

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Panorama Study

- **Study looking at treating pts with moderately severe to severe NPDR with serial Eylea**
  - **402 pts**
  - **Treated either q 8 or q 16 weeks for 2 yrs**
- **At 1 yr:**
  - **58% of pts overall had 2 line regression of DR vs 6% in sham**

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Proliferative Diabetic Retinopathy (PDR)

- Hallmark is retinal neovascularization
  - response to ischemia from capillary closure
  - grow onto lattice of vitreous
  - new vessels are fragile and easily rupture
- Neo divided into 2 categories
  - NVD: on or within 2 DD of optic disc
  - NVE: neovascularization elsewhere
- Follow-up: Retinal consult within 2-4 weeks

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High Risk PDR

- NVD >1/4 to 1/3 disc area
- Any NVD with a PRH or VH
- Moderate to severe NVE with VH or PRH
- Poses very high risk of severe VH and vision loss within 2 years
- Follow-up: Urgent Retinal consult (24-48 hours)

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Protocol S

- **Non-inferior study evaluating Lucentis vs. PRP**
- **55 sites, 203 pts with PRP, 191 with Lucentis, as frequent as q 4 weeks**
- **At 2 years:**
  - **VA improved 2.8 letters with Lucentis vs. 0.2 with PRP**
  - **More VF loss with PRP:. 531db vs. 213db loss**
  - **More vitrectomies in PRP group: 15% vs 4%**

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Protocol S

- Bottom line:
  - Longer Study needed
  - Economics may dictate
  - May be best with concurrent DME
  - Pt must be complaint
  - Perhaps combo of both treatments will be best?
  - Role in severe NPDR?

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DME

- **Old definitions being replaced with newer ones based on OCT findings**
  - **Center involved**
  - **Non-center involved**
  - **OCT best way to evaluate retina for DME**
- **DME responsible for more cases of moderate visual loss in pts with Type 2 DM than DR**
- **New treatments**

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antiVEGF

- **Lucentis, Avastin, Eylea**
- **Shown in multiple studies to be beneficial for DME**
  - **RISE**
    - **18.1% of pts in sham gained ≥ 15 letters vs. 44.8% (0.3 mg) or 39.2% (0.5 mg)**
    - **2.6 letters gained in sham vs. 12.5 (0.3mg) or 11.9 (0.5mg)**
  - **RIDE**
  - **READ**
  - **VISTA**
  - **VIVID**

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Protocol -T: Lucentis vs Avastin vs Eylea

- One year
  - Eylea gained 13.3 letters
  - Lucentis 11.2
  - Avastin 9.7
  - No statistical difference
- If VA was 20/50 or worse
  - Eylea gained 18.9
  - Lucentis 14.2
  - Avastin 11.8

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Protocol -T

- 2 year results
  - No statistically significant difference between 3 drugs, even in those worse than 20/50
    - But better acuity with Eylea
  - Bottom line:
    - It may matter which drug
    - May matter more with worse vision
    - Economics may dictate
      - In order to justify use of lucentis/eylea vs avastin, price would have to decrease by 70-80%

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Protocol V

- 702 pts with CI-DME with VA 20/25 or better
- 3 treatment groups
  - Eylea
  - FML
  - Observation
- At end of 2 years, rate of loss of 5 letters or more similar in all 3 groups
- Avg acuity in all 3 groups was 20/20
- Bottom line: pts with CI-DME and good VA can be observed

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Care of the diabetic patient

- Dilated retinal exams
- Timely intervention and referral to retinal specialist
  - CI-DME
  - PDR
  - Severe NPDR
- Patient education
  - inform of ocular side effects
  - retinopathy possible even with good vision
  - report ocular symptoms associated with DM
  - advise about organizations for support

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